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Predictors of mortality and treatment success during treatment for rifampicin-resistant tuberculosis within the South African National TB Programme, 2009 to 2011: a cohort analysis of the national case register

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SUMMARY

Background: The South African Electronic Drug-Resistant Tuberculosis Register (EDRweb) is the national database of registered drug-resistant tuberculosis (DR-TB) cases.
Methods: This study was a retrospective, de-identified secondary analysis of EDRweb patients initiating treatment for rifampicin-resistant TB (January 2009 to September 2011). The relative risks of death and treatment success were estimated using modified Poisson regression with robust error estimation.
Results: Seventeen thousand six hundred and ninety-seven cases of DR-TB were registered and met the inclusion criteria; 52.0% (n = 9207) were male and the median age was 35 years (interquartile range 27–43 years). Of the 9419 cases with HIV infection (53.2%), 7157 (76.0%) were on antiretroviral therapy. Most had undergone previous TB treatment (76.5%, n = 13 531). Multidrug-resistant TB was the most common diagnosis, at 80.6% (n = 14 272). No treatment outcome was available for 6934 patients (39.2%). For patients with outcomes, 4227 (39.4%) were successfully treated, 2987 (27.8%) died, 2533 (23.7%) were lost to follow-up, and 996 (9.3%) failed. Second-line drug resistance was the strongest predictor of death during DR-TB treatment; extensively drug-resistant TB patients were more likely to have died during treatment (adjusted relative risk 2.63, 95% confidence interval 2.45–2.84).
Conclusions: Testing for second-line drug resistance at initiation of DR-TB treatment can identify patients most at risk of treatment failure and death and most in need of individualized treatment.
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1. Introduction

According to the World Health Organization (WHO) Global Tuberculosis Report for 2014, South Africa was among the 10 highest drug-resistant tuberculosis (DR-TB) burden countries in the world when ranked by estimated burden of multidrug-resistant (MDR) TB cases.[1] In terms of the absolute number of cases diagnosed as rifampicin (RIF)-resistant TB, South Africa ranked fourth behind only China, India, and Russia.[1] The 2011 South African guidelines for the decentralization and deinstitutionalization of MDR-TB treatment have resulted in an increasing number of patients receiving second-line treatment for DR-TB each year. The number of patients who successfully completed DR-TB treatment was reported as 45% of the 2011 cohort.[1]

Since 2009, South Africa has maintained an electronic case register for DR-TB patients, the Electronic Drug-Resistant Tuberculosis Register (EDRweb). In order to inform policy and practice for improved DR-TB outcomes, patient and treatment characteristics reported within the EDRweb were analysed to determine predictors of treatment success or mortality during DR-TB treatment for patients registered from January 1, 2009 to September 30, 2011.

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2. Methods

A retrospective, de-identified secondary analysis of the routinely reported EDRweb database was conducted. TB and DR-TB are notifiable diseases in South Africa, and the National TB Programme (NTP) maintains national case registration databases. The EDRweb has been the electronic case registration database for the South African NTP since 2009; however, the paper-based registers were used for reporting to the WHO until 2012. A census of patients registered in the EDRweb from January 1, 2009 up to September 30, 2011, with follow-up until September 30, 2013, was exported for analysis (n = 22 152).

2.1. DR-TB treatment guidelines and case definitions 2009–2011

MDR-TB is defined as DR-TB that is resistant to RIF and isoniazid (INH). Although drug-sensitive TB can be diagnosed based upon clinical indications, South African guidelines require bacteriological laboratory confirmation of MDR-TB. At initiation of second-line treatment and if not improving clinically, a patient who has MDR-TB is tested for further anti-TB drug resistance. Resistance to RIF and INH plus any fluoroquinolone (FLQ) and any second-line injectable drug (SLID) is defined as extensively drug-resistant (XDR) TB. Resistance to RIF and INH and either a FLQ or a SLID is referred to as preXDR-TB. Until new guidelines were issued in 2011,[2] most South African DR-TB patients were treated as inpatients at specialized, provincial-level M/XDR-TB treatment centres.[2] South African NTP guidelines prior to 2011 indicated that patients with at least MDR-TB should be hospitalized for 6 months or until they achieved culture conversion, defined as two consecutive months with culture-negative sputa.[3]

The Xpert MTB/RIF test for the diagnosis of TB and RIF resistance was not available within the South African NTP during the study period. Patients at high risk of having DR-TB as a result of being a contact of a person with DR-TB, or due to failure to smear convert during TB treatment, were targeted for DR-TB testing. Diagnosis relied mainly on phenotypic drug sensitivity testing (DST) of culture isolates. The National Health Laboratory Service (NHLS) rolled out line probe assay (LPA) genotypic testing on culture isolates from 2009 to 2011,[4] and the results from LPA were reported for RIF and INH if available. DST was performed through the NHLS specialized laboratories for a panel of first-line drugs: RIF, INH, ethambutol (EMB), and streptomycin (SM). If at least MDR-TB, then a panel of second-line drugs would be tested: kanamycin (KM), ofloxacin (OFX), and ethionamide (ETO). Each panel of DST cultures took 6 to 12 weeks for results.

Patients with RIF resistance or MDR-TB were treated with a standardized regimen,[3] consisting of two phases. The 6-month intensive phase (usually hospitalized) included daily dosing of a SLID, KM, or amikacin (AM) and four additional oral drugs: OFX, EMB or ETO, terizidone (TZD), and pyrazinamide (PZA). The continuation phase of treatment included continuation of the regimen for 18 months following culture conversion, with the exception of the SLID. Patients with XDR-TB or documented resistance to either a FLQ or SLID (preXDR) could access individualized regimens including the SLID capreomycin, moxifloxacin (MFX), para-aminosalicylic acid (PAS), or clofazimine.

Outcomes of DR-TB treatment were assigned at the end of treatment (typically 24 months) and were defined at the time as: 'cured', i.e. completed treatment and culture-negative for five consecutive months in the last year of treatment; 'completed', i.e. completed treatment but did not meet the definition of cured; 'died', i.e. death due to any cause while on DR-TB treatment; 'default' (lost to treatment follow-up), i.e. treatment interrupted for two or more consecutive months; 'failure', i.e. two or more positive cultures out of the five consecutive cultures taken in the final year of treatment; or 'still on treatment' at the time of report.[3] Treatment success was defined as the sum of patients who were either cured or completed treatment.

2.2. HIV treatment guidelines 2009–2011

In April 2010, the South African guidelines for antiretroviral therapy (ART) were updated to indicate that all M/XDR-TB patients, regardless of CD4 count, were eligible for ART initiation and should be fast-tracked for initiation.[5] Prior to this (the 2004 guidelines), only patients who had a CD4 count of <200 cells/mm^3 were eligible and there was uncertainty as to the timing of initiation of ART for TB patients.[6]

2.3. EDRweb and data extraction

De-duplication and cleaning of the register was done as per the standard policies and procedures of the NTP prior to export. Follow-up data were censored at September 30, 2013. All patient records included in the study had at least 24 months of follow-up time. All patient identifiers were removed during the export process. Patients were excluded if they had no record of initiating DR-TB treatment within EDRweb (n = 3743). Patients who were reported to have only mono-resistant TB and no laboratory RIF result (i.e., mono-INH-resistant, n = 462), who were reported as transfer-in (n = 223), or who were missing a DR-TB diagnosis (n = 27), were also excluded from the analysis. Thus, only patients with at least RIF-resistant TB were included in the analysis.

Patient and treatment characteristics analysed included age, sex, history of previous TB treatment, year of registration, TB foci (extrapulmonary or pulmonary), reported drug resistance, diagnosis of drug-resistant TB, HIV status, baseline smear and culture results, and DR-TB treatment. Age at registration was categorized as <15, 15–29, 30–44, 45–59, and 60 years and older.

Each patient could have multiple DST result sets reported. Each entry was numbered, with the month of testing reported (month 0 for treatment initiation, month 1 after 1 month of treatment, etc.), date of sputum collection, laboratory specimen number, and the drugs that had a resistant outcome. Drugs that were tested that had a sensitive, non-viable isolate, or contaminated result, were not reported. For the analysis, month 0 reports were defined as baseline.

Patient diagnosis was reported in the dataset as one of MDR-TB, mono- or poly-resistant DR-TB, or XDR-TB. For the analysis, if a patient was diagnosed as MDR-TB and had a reported DST result of resistance to a FLQ or a SLID, this was categorized as preXDR-TB.

Each patient could have multiple HIV tests reported. Each entry was numbered, with the date of testing and results. Additionally, HIV status was reported as a separate variable, presumably to incorporate patients with known HIV status who were not tested and counselled for HIV during DR-TB treatment. Any report of the patient being HIV-infected was recorded as the patient being HIV-infected. If no tests were reported as HIV-positive and there was at least one HIV report of being HIV-negative, the patient was recorded as HIV-negative. ART started was a 'yes/no' variable. Patients were categorized as HIV-negative, HIV-positive on ART, HIV-positive not on ART or ART status unknown, or HIV status unknown.

Each patient had multiple monthly sputum smear microscopy and sputum culture tests reported – up to 40 entries. Smear status was reported as negative or positive, but no specific grading (i.e. scant, +, ++, +++) was given. There was also a report of an 'initial' smear and culture result (defined as being taken prior to referral to the DR-TB unit) and a 'baseline' smear and culture result (defined as the sputum specimen taken on admission to the DR-TB unit). A positive smear result in the baseline, initial, or month 0 report was defined as smear-positive at baseline for the analysis; the same definition and method was applied to establish baseline culture results.

Second-line TB drugs were recorded in EDRweb as a list of drugs that may have been prescribed for either the intensive or continuation phase, or because of a regimen change during treatment. Doses, the duration of treatment, and the reasons for treatment changes are not reported within EDRweb.

One treatment outcome is retained in EDRweb with one outcome date; the outcome may be changed after cohort reporting (e.g., 24-month outcomes reported to the WHO). The treatment outcome date reflected the date of reporting or assignment of the outcome at 24 months. For death, treatment failure, and loss to follow-up, the outcome date was defined as the date the patient was last at the facility, not necessarily the date of the event.

2.4. Statistical analysis

All analyses were conducted in Stata SE version 13 (StataCorp., College Station, TX, USA). Patient and treatment characteristics were recorded using the median and interquartile range (IQR) for continuous variables, and the frequency and proportion for categorical variables. Predictors of treatment outcome (either treatment success or death) were estimated using modified Poisson regression with robust standard errors to produce relative risks (risk ratios, or RR);[7] these were reported with the corresponding 95% confidence intervals (CI). The univariate and adjusted (multivariate) results are presented.

2.5. Ethics

Ethical approval for this de-identified, retrospective secondary analysis of routinely reported patient-level data was received from the Human Research Ethics Committee of the University of the Witwatersrand.

3. Results

3.1. DR-TB patient characteristics

Patient characteristics are summarized in Table 1. Seventeen thousand six hundred and ninety-seven cases of DR-TB were registered between January 2009 and September 2011, met the inclusion criteria, and were included in the baseline analysis (Figure 1). Approximately half of the patients were male (52.0%), and the median age was 35 years. Of the 9419 patients with reported HIV infection (53.2%), 7157 (76.0%) were on ART.

Less than half of the patients were smear microscopy-positive at 'baseline' (n = 8076, 45.6%), although HIV-uninfected patients were more likely to be smear microscopy-positive (52.8%) than HIV-infected patients (45.0%) (Chi-square difference of proportions, $p < 0.000$). A positive sputum culture at baseline was reported for 70.0% (n = 12 386) of patients; 10.3% were culture-negative at baseline and 19.7% of patients were either missing culture results or culture was contaminated.

3.2. DR-TB diagnosis and treatment

MDR-TB was the most common diagnosis in the cohort, at 80.6% (n = 14 272), including 4.3% (n = 617) of patients with preXDR-TB; 9.5% of patients were RIF-mono-resistant and 9.8% of patients had XDR-TB (Table 2).

Just over half of the MDR-TB patients (56.3%) were reported as receiving at least the standard regimen (KM/AM, OFX, ETO, TZD, PZA). Most (89.9%) XDR-TB patients were on individualized regimens containing PAS (79.2%), capreomycin (73.8%), and/or MFX (49.9%). Almost all patients, regardless of diagnosis, received a SLID (93.9%), FLQ (92.7%), ETO (91.6%), and PZA (95.1%).

Table 1
Baseline descriptive characteristics of RIF-resistant TB patients registered in EDRweb from January 1, 2009 to September 30, 2011

Characteristic	Count	Proportion %
All patients	(N = 17 697)	
Gender		
Male	9207	52.0%
Female	8406	47.5%
Missing	84	0.5%
Age, years	Median: 35	IQR: 27–43
<15	526	3.0%
15–29	5171	29.2%
30–44	8068	45.6%
45–59	3396	19.2%
60+	536	3.0%
HIV status		
HIV-infected	9419	53.2%
HIV-negative	4770	27.0%
HIV status unknown, missing	3508	19.8%
Antiretroviral therapy		
On ART (before or during DR-TB)	7157	76.0%
Not on ART	918	9.7%
ART status missing	1344	14.3%
Previously treated for TB		
New patient	4161	23.5%
History of TB treatment	13 531	76.5%
TB foci		
Pulmonary TB	15 910	89.9%
Extrapulmonary TB	178	1.0%
Not reported, missing	1609	9.1%
Sputum smear microscopy at baseline[a]		
AFB-positive	8076	45.6%
AFB-negative	6286	35.5%
Not reported or error	3335	18.8%
Sputum culture at baseline[a]		
MTB-positive	12 386	70.0%
Negative	1828	10.3%
Not reported or contaminated	3483	19.7%

RIF, rifampicin; TB, tuberculosis; EDRweb, South African Electronic Drug-Resistant Tuberculosis Register; IQR, interquartile range; ART, antiretroviral therapy; DR-TB, drug-resistant tuberculosis; AFB, acid-fast bacilli; MTB, *Mycobacterium tuberculosis*.
[a] A positive smear result in the baseline, initial, or month 0 report was defined as smear-positive at baseline for the analysis; the same definition and method was applied to establish baseline culture results.

3.3. DR-TB treatment outcomes

Treatment outcomes reported in EDRweb as of September 2013 are presented in Table 3. No outcome was reported for 39.2%

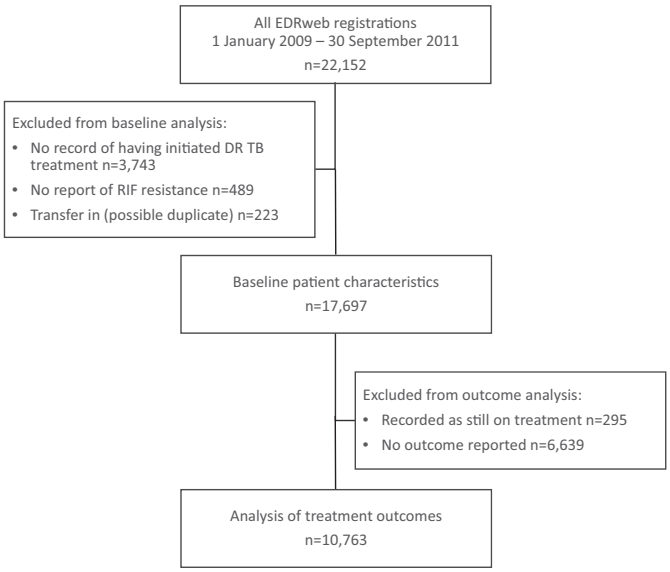

Figure 1. Patients included in the analysis of baseline characteristics and reported outcomes.

Table 2
Diagnosis and treatment of RIF-resistant TB patients in EDRweb (January 1, 2009 to September 30, 2011)

Characteristic	Count (N = 17 697)	Proportion %
DR-TB diagnosis		
RIF mono-resistant TB	1671	9.5%
MDR-TB (resistant to RIF and INH)	14 272	80.6%
MDR-TB without second-line resistance	13 655	77.2%
PreXDR-TB SLID	391	2.2%
PreXDR-TB FLQ	226	1.3%
XDR-TB (MDR-TB plus SLID and FLQ)	1741	9.8%
Year of registration		
2009	5457	30.8%
2010	6613	37.4%
2011 (censored at September 30, 2011)	5627	31.8%
DST resistance reported		
Rifampicin (RIF)-resistant	15 442	87.3%
Isoniazid (INH)-resistant	13 514	76.4%
Ethambutol (EMB)-resistant	1563	8.8%
Streptomycin (SM)-resistant	3803	21.5%
Kanamycin (KM)-resistant	662	3.7%
Amikacin (AM)-resistant	1046	6.5%
Ofloxacin (OFX)-resistant	1313	7.4%
Second-line treatment[a]		
Amikacin (AM)	2780	15.7%
Kanamycin (KM)	12 333	69.7%
Capreomycin (CM)	1653	9.3%
Any second-line injectable drug (SLID)	16 625	93.9%
Ofloxacin (OFX)	14 555	82.3%
Moxifloxacin (MFX)	1909	10.8%
Any fluoroquinolone (FLQ)	16 410	92.7%
Ethambutol (EMB)	11 576	65.4%
Para-aminosalicylic acid (PAS)	1838	10.4%
Terizidone (TZD)	12 976	73.3%
Pyrazinamide (PZA)	16 835	95.1%
Ethionamide (ETO)	16 215	91.6%

RIF, rifampicin; TB, tuberculosis; EDRweb, South African Electronic Drug-Resistant Tuberculosis Register; DR-TB, drug-resistant tuberculosis; MDR-TB, multidrug-resistant tuberculosis; INH, isoniazid; XDR-TB, extensively drug-resistant tuberculosis; SLID, second-line injectable drug; FLQ, fluoroquinolone; DST, drug sensitivity testing.

[a] Only standard regimen or drugs reported to be used in more than 1000 patients are listed; reported drugs not listed above: clofazimine (n = 114, 0.6%), ciprofloxacin (n = 326, 1.8%), isoniazid (n = 762, 4.3%), rifampicin (n = 186, 1.1%), streptomycin (n = 70, 0.3%), levofloxacin (n = 16, 0.1%), prothionamide (n = 26, 0.1%), clarithromycin (n = 125, 0.7%), amoxicillin (n = 115, 0.6%), and cycloserine (n = 17, 0.1%).

(n = 6934) of all patients in the cohort. Patients who initiated treatment in 2011 were less likely to have treatment outcomes ($p < 0.05$).

For patients with outcomes, treatment success was the most common outcome, at 39.4% (cured 27.5% (n = 2695) and completed treatment 11.8% (n = 1262)). Unsuccessful outcomes were the following: 27.8% died, 23.7% were lost to follow-up, and 9.3% failed treatment. For XDR-TB patients with outcomes (n = 1076), 60.8% (n = 654) died during treatment. XDR-TB treatment success across the three years of case registration was 12.7% (n = 137).

3.4. Relative risk of death during DR-TB treatment

Second-line drug resistance was the strongest predictor of death during DR-TB treatment (Table 4). Patients who had XDR-TB (adjusted RR (aRR) 2.63, 95% CI 2.45–2.84) and those who had preXDR-TB FLQ (aRR 1.56, 95% CI 1.23–1.98) or preXDR-TB SLID (aRR 1.63, 95% CI 1.38–1.94) were all more likely than those who did not have documented second-line drug resistance to have died during treatment.

Compared to patients known to be HIV-negative, patients who were HIV-infected and not on ART or with ART status unknown, were nearly twice as likely to die (aRR 1.90, 95% CI 1.69–2.14). Those who were HIV-infected on ART and with unknown HIV status had similar risks of mortality – aRR 1.54 (95% CI 1.41–1.69) and aRR 1.66 (95% CI 1.48–1.86), respectively.

Baseline smear positivity (aRR 1.47, 95% CI 1.36–1.59) and prior TB treatment (aRR 1.16, 95% CI 1.06–1.27) were both associated with a higher relative risk of mortality. Patients aged <15 years were 36% less likely to die (aRR 0.64, 95% CI 0.48–0.87), while patients aged ≥60 years were more likely to die (aRR 1.83, 95% CI 1.56–2.15) compared to patients aged 45–59 years. No statistically significant differences in mortality were associated with sex, treatment with FLQ or SLID, or year of treatment initiation.

3.5. Relative risk of successful DR-TB treatment

The absence of reported second-line drug resistance was the strongest predictor of successful treatment (Table 5). Patients who had XDR-TB (aRR 0.31, 95% CI 0.26–0.36) and those who had preXDR SLID (aRR 0.48, 95% CI 0.38–0.61) or preXDR FLQ (aRR 0.51, 95% CI 0.37–0.69) were all significantly less likely to have either completed treatment or been cured.

HIV-infected patients on ART were as likely to be successfully treated as HIV-negative patients (aRR 0.98, 95% CI 0.92–1.03). HIV-infected patients not on ART or ART status missing were 19% less likely than HIV-negative patients to have a successful outcome (aRR 0.81, 95% CI 0.74–0.88).

Males were less likely to successfully complete treatment compared to females (aRR 0.83, 95% CI 0.79–0.87). Patients who were smear microscopy- and culture-positive at baseline were less likely to successfully complete treatment compared to those with negative results (aRR 0.81, 95% CI 0.77–0.85, and aRR 0.80, 95% CI 0.75–0.85, respectively). Children <15 years old were 1.32 times more likely to have successful outcomes than patients aged 45–59 years (95% CI 1.18–1.48).

Table 3
Treatment outcomes as of September 30, 2013 for RIF-resistant TB patients in EDRweb, by diagnosis category

Outcome	All patients	RIF-resistant[a]	MDR-TB	PreXDR-TB[b]	XDR-TB
All patients	n = 17 697	n = 1684	n = 13 655	n = 617	n = 1741
All outcomes	n = 10 763 (60.8%)	n = 818 (48.6%)	n = 8433 (61.8%)	n = 436 (70.7%)	n = 1076 (61.8%)
Cured	2965 (27.5%)	276 (33.7%)	2528 (30.0%)	61 (14.0%)	100 (9.3%)
Completed	1262 (11.8%)	94 (11.5%)	1104 (13.1%)	27 (6.2%)	37 (3.4%)
Successful	4227 (39.4%)	370 (45.2%)	3720 (44.1%)	88 (20.2%)	137 (12.7%)
Died	2987 (27.8%)	157 (19.2%)	2008 (23.8%)	168 (38.5%)	654 (60.8%)
Lost to follow-up	2553 (23.7%)	241 (29.5%)	2109 (25.0%)	58 (13.3%)	145 (13.5%)
Treatment failure	996 (9.3%)	50 (6.1%)	684 (8.1%)	122 (28.0%)	140 (13.0%)
Missing outcome[c]	n = 6934 (39.2%)	n = 866 (51.4%)	n = 5222 (38.2%)	n = 181 (29.3%)	n = 665 (38.2%)

RIF, rifampicin; TB, tuberculosis; EDRweb, South African Electronic Drug-Resistant Tuberculosis Register; MDR-TB, multidrug-resistant tuberculosis; XDR-TB, extensively drug-resistant tuberculosis; INH, isoniazid; DST, drug sensitivity testing.

[a] Includes both cases that were confirmed mono-RIF-resistant and cases that were diagnosed RIF-resistant but with INH sensitivity not confirmed.

[b] Case registration reported as having MDR-TB and having reported DST resistance to either a fluoroquinolone or a second-line injectable.

[c] Cases reported as being 'still on treatment' were categorized as missing the 'final' outcome.

Table 4
Relative risk of death during DR-TB treatment, by patient and treatment characteristics[a]

	RR	95% CI	Adjusted RR[b]	95% CI
Male	0.95	0.89–1.01	0.98	0.92–1.05
Treatment included SLID	0.88	0.77–1.00	1.02	0.88–1.19
Treatment included FLQ	0.68	0.62–0.75	0.91	0.81–1.01
Second-line drug resistance				
RIF or MDR (no second-line resistance)	Ref.		Ref.	
Resistant to SLID	1.69	1.45–1.96	1.63	1.38–1.94
Resistant to FLQ	1.53	1.23–1.89	1.56	1.23–1.98
XDR-TB	2.59	2.44–2.75	2.63	2.45–2.84
History of TB treatment	1.25	1.16–1.36	1.16	1.06–1.27
HIV-status				
HIV-negative	Ref.		Ref.	
HIV-infected, on ART	1.51	1.40–1.64	1.54	1.41–1.69
HIV-infected, not on ART	1.70	1.53–1.88	1.90	1.69–2.14
HIV unknown	1.68	1.52–1.85	1.66	1.48–1.86
Smear microscopy positive at baseline[c]	1.58	1.46–1.70	1.47	1.36–1.59
Sputum culture positive at baseline[c]	1.48	1.28–1.71	1.16	1.00–1.35
Age group, years				
<15	0.65	0.50–0.85	0.64	0.48–0.87
15–29	0.80	0.73–0.87	0.78	0.71–0.87
30–44	0.92	0.85–1.00	0.85	0.78–0.93
45–59	Ref.		Ref.	
60+	1.47	1.28–1.68	1.83	1.56–2.15
Registration year				
2009	Ref.		Ref.	
2010	1.05	0.97–1.13	1.04	0.96–1.13
2011	1.08	1.00–1.17	1.08	0.98–1.18

DR-TB, drug-resistant tuberculosis; RR, relative risk; CI, confidence interval; SLID, second-line injectable drug; FLQ, fluoroquinolone; RIF, rifampicin; MDR, multi-drug-resistant; XDR-TB, extensively drug-resistant tuberculosis; ART, antiretroviral therapy.
[a] Relative risk (risk ratio) calculated using Poisson regression with robust standard errors.
[b] Adjusted for all other factors in the table.
[c] A positive smear result in the baseline, initial, or a month 0 report was defined as smear-positive at baseline for the analysis; the same definition and method was applied to establish baseline culture results.

Table 5
Relative risk of treatment success during DR-TB treatment, by patient and treatment characteristics[a]

	RR	95% CI	Adjusted RR[b]	95% CI
Male	0.86	0.82–0.90	0.83	0.79–0.87
Treatment included SLID	1.00	0.89–1.12	0.92	0.83–1.03
Treatment included FLQ	1.12	1.01–1.24	0.92	0.83–1.02
Second-line drug resistance				
RIF or MDR (no second-line resistance)	Ref.		Ref.	
Resistant to SLID	0.45	0.35–0.57	0.48	0.38–0.61
Resistant to FLQ	0.49	0.36–0.66	0.51	0.37–0.69
XDR-TB	0.29	0.25–0.34	0.31	0.26–0.36
History of TB treatment	0.84	0.80–0.88	0.91	0.86–0.96
HIV-status				
HIV-negative	Ref.		Ref.	
HIV-infected, on ART	1.03	0.97–1.08	0.98	0.92–1.03
HIV-infected, not on ART	0.86	0.79–0.94	0.81	0.74–0.88
HIV unknown	0.98	0.91–1.05	0.80	0.89–1.03
Smear microscopy positive at baseline[c]	0.73	0.69–0.76	0.81	0.77–0.85
Sputum culture positive at baseline[c]	0.68	0.64–0.73	0.80	0.75–0.85
Age group, years				
<15	1.56	1.40–1.75	1.32	1.18–1.48
15–29	0.91	0.85–0.98	0.85	0.79–0.91
30–44	0.97	0.91–1.03	0.94	0.88–1.00
45–59	Ref.		Ref.	
60+	0.84	0.72–0.98	0.84	0.72–0.97
Registration year				
2009	Ref.		Ref.	
2010	0.98	0.93–1.04	1.00	0.95–1.07
2011	0.92	0.87–0.98	0.95	0.90–1.01

DR-TB, drug-resistant tuberculosis; RR, relative risk; CI, confidence interval; SLID, second-line injectable drug; FLQ, fluoroquinolone; RIF, rifampicin; MDR, multi-drug-resistant; XDR-TB, extensively drug-resistant tuberculosis; ART, antiretroviral therapy.
[a] Relative risk (risk ratio) calculated using Poisson regression with robust standard errors.
[b] Adjusted for all other factors in the table.
[c] A positive smear result in the baseline, initial, or a month 0 report was defined as smear-positive at baseline for the analysis; the same definition and method was applied to establish baseline culture results.

A prior history of TB treatment was statistically significant but moderate in impact (aRR 0.91, 95% CI 0.86–0.96). Treatment with either a SLID or a FLQ and year of registration were not statistically significant predictors of success.

4. Discussion

Since 2009, South Africa has maintained the EDRweb for routine reporting of all DR-TB patients treated within the South African NTP. The 17 697 cases of DR-TB registered between January 1, 2009 and September 30, 2011 represent one of the largest cohorts of DR-TB patients on treatment in the world.

A 2009 systematic review of global MDR-TB treatment outcomes reported a pooled treatment success rate of 62%;[8] DR-TB treatment success was reported by the WHO as 48% for the 2011 global cohort.[1] For the same year, South Africa reported a treatment success rate of 45%.[1] Because of censoring in the data extract, updating of treatment outcomes since reporting, and verification of reporting against paper reports, the EDRweb export analysed here cannot be compared directly to the WHO reported cohorts. However, having information about the patient and treatment characteristics can increase our understanding of the outcomes reported.

Approximately half of the patients in EDRweb were reported as HIV-infected (53.2%), with most HIV-infected patients being on ART (76.0%). HIV-infected patients not on ART were nearly two times more likely to die than HIV-negative patients (aRR 1.90). A low CD4 count (especially $\leq$100 cells/mm^3) is a known predictor of mortality for persons who are HIV-infected,[9] but only 5.4% of HIV-infected patients had a CD4 count reported in EDRweb. In 2010, South Africa changed its ART guidelines based upon evidence that early ART initiation during TB treatment could reduce mortality.[5,6] The change in guidelines occurred during the period analysed here, and the non-significant difference in risk of success for patients who are on ART compared to the HIV-negative (aRR 0.98) found in this study is encouraging. Because the duration on ART and baseline CD4 are important clinical indicators for persons with HIV, improved capturing of this information in the national database could improve the management of these patients.

The strongest predictor of mortality in this cohort was not HIV infection, but resistance to the most effective second-line drugs in the treatment regimen: preXDR SLID (aRR 1.63), preXDR FLQ (aRR 1.56), or both (XDR-TB, aRR 2.63). This finding should add weight to recommendations proposing that all DR-TB patients be tested for additional resistance at treatment initiation and highlights the need for new classes of second-line TB treatment.[1]

Patients initiating DR-TB treatment in 2011 in the South African NTP had earlier access to ART,[5] expanded access to rapid molecular detection of INH and RIF resistance,[4] and potential access to the fourth-generation FLQ MFX.[10] New guidelines issued in 2011 also decentralized MDR-TB treatment,[2] which meant that patients may have been able to access appropriate treatment earlier.[11] However, the impact of these changes could not be detected in the EDRweb data, which were censored at September 30, 2011. DR-TB treatment registration in 2011 compared to 2009 was not a

significant predictor of treatment success (aRR 0.95). The analysis should be repeated with the complete 2011 cohort and 2012 cohort before conclusions can be drawn regarding the impact of the improvements in DR-TB diagnosis, treatment, and treatment access introduced in 2011.

Many of the patient and treatment characteristics have associations and relationships among themselves, e.g., HIV infection was found to be associated with negative baseline smear microscopy and DST for second-line drug resistance, which can only be done if a patient has a positive baseline culture. Yet, the adjusted model for both relative risk of mortality and treatment success showed little difference to the unadjusted model. The robustness of the relative risk for mortality for patients with second-line drug resistance even when holding HIV status, sputum smear status, treatment regimen, age, and sex constant, emphasizes the importance of this finding. Eleven percent (n = 1996) of the cohort did not have any DST results reported within EDRweb. An additional 61.3% of the cohort had reported resistance to only INH and/or RIF. Expanding the reporting requirement to include sensitive DST results would help us to identify those patients within this 61.3% who were tested and were sensitive to second-line drugs and how many never accessed second-line DST.

There are limitations to this study. This was a retrospective, de-identified secondary cohort analysis of routinely reported data. Reporting requirements were not necessarily designed to provide information to answer research questions. Gaps in reporting could not be addressed by file review or contacting patients. The missing information on treatment outcome (39.2% of the cohort without a treatment outcome) is the biggest limitation of the data. The treating clinician is responsible for assigning outcomes; information extracted from medical files and reported within EDRweb is not sufficient for outcomes to be assigned without additional patient file review. Recognizing the high number of patients without outcomes, the South African NTP has been leading a process of training, guidelines, and data-cleaning.

Another possible limitation is the analysis of a de-identified extract of EDRweb. Use of a unique patient identifier was not government policy during the period of analysis and therefore duplicate registrations may have been included. However, treatment sites were centralized at a provincial level and efforts are made within the NTP standard reporting procedures to match patients using names, addresses, and dates of birth; therefore duplication is not likely to be a significant source of bias in this cohort.

During the study period, the Xpert MTB/RIF test was not in use in South Africa and testing for RIF resistance was not universal. Patients with a history of TB treatment were prioritized for resistance testing and this may have led to an over-estimation of persons with prior TB as a proportion of persons with DR-TB in South Africa. Analysis of cohorts initiated from 2013 after roll-out of Xpert MTB/RIF as the initial TB diagnostic was complete, as well as the results of the recently completed national TB drug resistance surveillance, should better inform our understanding of whether DR-TB is transmitted or acquired in this context.

Only patients who have initiated RIF-resistant DR-TB treatment are routinely reported in EDRweb. A substantial proportion of patients diagnosed during this period were not initiated on treatment,[12] and MDR-TB and XDR-TB with HIV co-infection have been shown to have a high early mortality rate in this setting.[13] Therefore, these findings can only be applied to patients who were diagnosed and survived until treatment initiation, not to all persons with DR-TB in South Africa.

In conclusion, the diagnosis of XDR-TB and reported resistance to two effective classes of second-line TB drugs – the fluoroquinolones and second-line injectable drugs – are the strongest predictors of mortality during DR-TB treatment and poor rates of treatment success. Interventions targeted at identifying and treating this additional resistance, such as universal testing of all DR-TB patients for second-line drug resistance, the use of rapid genotypic diagnostic tests to screen for second-line drug resistance, and increased access to new classes of second-line TB treatment (such as linezolid, bedaquiline, delamanid, and pretomanid), could be effective in reducing mortality and improving the rate of treatment success in South Africa's National TB Programme.

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References

1. World Health Organization. Global tuberculosis report 2014. Geneva: WHO; 2014. Available at: www.who.int/tb/publications/global_report/en/ (accessed 1 June 2015)
2. Directorate of Drug-Resistant TB, TB, and HIV. Multi-drug resistant tuberculosis: a policy framework on decentralised and deinstitutionalised management for South Africa. Pretoria: South African Department of Health; 2011.
3. Directorate of Tuberculosis Control. Management of drug-resistant tuberculosis in South Africa: Policy guidelines. Pretoria: South African Department of Health; 2007.
4. Hanrahan CF, Dorman SE, Erasmus L, Koornhof H, Coetzee GJ, Golub JE. The impact of expanded testing for multidrug resistant tuberculosis using genotype MTBDRplus in South Africa: an observational cohort study. *PLoS One* 2012;**7**(11):e49898. http://dx.doi.org/10.1371/journal.pone.0049898. Epub 2012 Nov 30.
5. South African Department of Health. Clinical guidelines for the management of HIV and AIDS in adults and adolescents. Pretoria: South African Department of Health; 2010. Available at: http://www.sahivsoc.org/upload/documents/Clinical_Guidelines_for_the_Management_of_HIV_AIDS_in_Adults_Adolescents_2010.pdf (accessed 1 June 2015).
6. Havlir DV, Kendall MA, Ive P, Kumwenda J, Swindells S, Qasba SS, et al. Timing of antiretroviral therapy for HIV-1 infection and tuberculosis. *N Engl J Med* 2011;**365**:1482–91.
7. Zou G. A modified Poisson regression approach to prospective studies with binary data. *Am J Epidemiol* 2004;**159**:702–6.
8. Orenstein EW, Basu S, Shah NS, Andrews JR, Friedland GH, Moll AP, et al. Treatment outcomes among patients with multidrug-resistant tuberculosis: systematic review and meta-analysis. *Lancet Infect Dis* 2009;**9**:153–61.
9. Gupta A, Nadkarni G, Yang W, Chandrasekhar A, Gupte N, Gregory P, et al. Early mortality in adults initiating antiretroviral therapy (ART) in low- and middle-income countries (LMIC): a systematic review and meta-analysis. *PLoS One* 2011;**6**(12):e28691. http://dx.doi.org/10.1371/journal.pone.0028691. Epub 2011 Dec 29.
10. Directorate of Drug-Resistant TB, TB, and HIV. Management of drug-resistant tuberculosis: policy guidelines. Pretoria: South African Department of Health; 2011. Available at: http://www.hst.org.za/publications/management-drug-resistant-tuberculosis-policy-guidelines (accessed 1 June 2015).
11. Loveday M, Wallengren K, Voce A, Margot B, Reddy T. Comparing early treatment outcomes of MDR-TB in a decentralized setting in KwaZulu-Natal, South Africa. *Int J Tuberc Lung Dis* 2012;**16**:209–15.
12. Ebonwu JI, Tint KS, Ihekweazu C. Low treatment initiation rates among multi-drug-resistant tuberculosis patients in Gauteng, South Africa, 2011. *Int J Tuberc Lung Dis* 2013;**17**:1043–8.
13. Gandhi NR, Shah NS, Andrews JR, Vella V, Moll AP, Scott M, et al. HIV coinfection in multidrug- and extensively drug-resistant tuberculosis results in high early mortality. *Am J Respir Crit Care Med* 2010;**181**:80–6.